Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

BIIB080 – MAPT$_{RX}$ ASO

Evidence Summary

BIIB080 decreases total and phosphorylated tau. No serious adverse events have been seen. It is administered intrathecally, but the effects are durable. Effects on cognition and function are unknown.

Neuroprotective Benefit: BIIB080 robustly and durably decreases total and phosphorylated tau in CSF. The clinical effects of this reduction are not known.

Aging and related health concerns: The physiological function of tau and effects of tau knockdown outside the central and peripheral nervous system are not well understood.

Safety: In the initial in-human study, BIIB080 appeared to be well-tolerated, with no drug-related serious events. Long-term effects of tau knockdown are not known.

Availability: In clinical development	**Dose**: Intrathecal doses from 10 to 115 mg have been tested; still selecting best dose.	**Sequence:** 5'-ccogttTTCTTACCacocct-3' "Capital letters represent 2'-deoxyribose nucleosides, and small letters 2'-(2-methoxyethyl)ribose nucleosides. Nucleoside linkages represented with a subscript o are phosphodiester, and all others are phosphorothioate. Letters represent adenine, 5-methylcytosine, guanine and thymine nucleobases." Source: Mummery et al., 2023
Half-life: Not published, but 'long'. In some regimens, it can be detected for at least 84 days after last dose.	**BBB**: Not penetrant; administered intrathecally	
Clinical trials: BIIB080 has been tested in one completed trial of 46 patients; a study of 735 patients is ongoing.	**Observational studies**: No observational studies of BIIB080 or other MAPT ASO have been completed.	

What is it?

Genes are transcribed into complementary RNA sequences known as pre-mRNA. Pre-mRNA then goes through a process known as splicing, where non-coding portions called introns are removed and coding portions called exons put together. Some genes can be alternatively spliced, meaning that they have different combinations of exons. Once spliced, the pre-mRNA is known as mRNA, and can be translated into protein (Clancy et al., 2008). Tau is encoded by the microtubule-associated protein tau (*MAPT*) gene. There are six known isoforms of tau that have different portions of the *MAPT* gene. The importance and impact of the different isoforms of tau is an area of active research (Wang & Mandelkow, 2016).

Tau is enriched in the axonal compartment of neurons. In the axon, tau is involved with regulation of microtubules, including microtubule assembly and stabilization. Tau is thought to be involved in other neuronal functions, including modulating neuronal activity, synaptic plasticity, and neurogenesis (Wang & Mandelkow, 2016).

Hyperphosphorylated or aggregated tau are pathological hallmarks of a family of diseases known as tauopathies; in these diseases, intracellular tau aggregates known as neurofibrillary tangles (NFTs) are formed. NFT burden is correlated with cognitive decline in AD patients (Mummery et al., 2023). Mutations in tau are also known to cause certain cases of tauopathies such as frontotemporal dementia

(FTD) and progressive supranuclear palsy (PSP) (Wang & Mandelkow, 2016). Strategies to modulate tau are therefore of great interest to the field.

As reviewed by Rinaldi and Wood, 2017, antisense oligonucleotides (ASO) are chemically modified synthetic oligonucleotides that are complementary to specific stretches of RNA. Once bound, the ASO can influence the fate of the RNA depending on the specific design of the ASO and the sequence it targets. The ASO can target the mRNA for destruction through ribonuclease H (RNase H), which degrades the RNA portion of RNA-DNA hybrids like mRNA-ASOs. The ASO can also physically block machinery necessary for translation of the entire mRNA or splicing machinery necessary for inclusion of a target exon. ASO binding can even be designed to increase translation of the mRNA into protein.

Several ASOs against tau have been studied. BIIB080, also known as $MAPT_{RX}$, is an ASO that is complementary to an 18-base stretch of intron 9 in the MAPT pre-mRNA. This is the only MAPT ASO that has completed any trial in humans. Upon binding, BIIB080 targets the pre-mRNA for degradation through RNase H1, which reduces translation of the tau protein (Mummery et al., 2023).

Neuroprotective Benefit: BIIB080 robustly and durably decreases total and phosphorylated tau in CSF. The clinical effects of this reduction are not known.

Types of evidence:

- 1 randomized controlled trial
- 3 commentaries on the randomized controlled trial
- 1 brief communication
- 1 poster presentation
- 5 reviews
- 5 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have yet been done in healthy patients to prevent dementia or decline.

Human research to suggest benefits to patients with dementia:

BIIB080 has been tested in a randomized, placebo-controlled multiple ascending dose (MAD) phase 1b study, with a follow-up period and long term extension (LTE) (Mummery et al., 2023). The study enrolled 46 patients with mild Alzheimer's disease and randomized 3:1 to BIIB080 or placebo. The treatment period was 13 weeks, and the follow up treatment period was 23 weeks. The LTE option began partway

through the study. The first two cohorts who received lower doses of BIIB080 therefore had variable start times before the LTE, whereas the second two cohorts who received higher doses of BIIB080 transitioned directly into the LTE after the follow-up period. The study endpoints were safety and tolerability; exploratory endpoints included CSF tau and tau PET.

In the MAD portion, the authors tested multiple intrathecal doses (10, 30, 60, and 115 mg) and different dosing schedules (every 4 weeks; every 12 weeks). In the LTE study, all groups received quarterly doses of either 60 or 115 mg, as the MAD portion indicated that the ASO was amenable to quarterly dosing and that these doses were well tolerated. The trial enrolled in cohorts, with each cohort having a successively higher dose. The groups were generally well-balanced, though Cohort C and Cohort D, corresponding to the 60 and 115 mg dose, respectively, had lower CDR-SB scores as there was an amendment during the study to enroll patients with lower CDR-SB scores. One other point to note is that the patients were on the younger side, with an average age of 66 years.

The authors observed BIIB080 in CSF from all treated patients and found a general increase of BIIB080 concentration over time, which they ascribe to the long half-life and slow clearance of BIIB080.

An important exploratory measure was the concentration of total tau in CSF over the course of the study. The study found dose-dependent and durable decreases in CSF total tau, with tau levels continuing to decrease after dosing ended. Eight weeks after the last dose of the MAD portion of the study, the average decrease in CSF total tau was −30%, −40%, −49% and −42% in the BIIB080 10 mg, 30 mg and 60 mg monthly and 115 mg quarterly groups, respectively. In the 60 and 115 mg groups, which had similar cumulative doses and continued directly into the LTE study portion, the CSF total tau reduction from baseline was 56% and 51% at 24 weeks after the last dose. This mechanistically fits, as tau is a long-lived protein, and as the ASO treatment only reduces production of new tau protein rather than affecting existing tau protein.

There were also similar decreases in both CSF p-tau181. At 8 weeks post last dose, the mean change from baseline was −35%, −44%, −52% and −49% in the BIIB080 10 mg, 30 mg and 60 mg monthly and 115 mg quarterly groups, respectively. At 24 weeks post last dose, the mean change in the 60 and 115 mg BIIB080 groups was −56% and −46%, respectively. The concentration of CSF total tau and p-tau181 was stable in the placebo group.

There were no group differences in the slight declines on measures of functional, cognitive, neurological, and psychiatric performance, and declines were as expected for patients with mild AD. Exploratory CSF assays of change from baseline included neurofilament light (NfL), neurofilament heavy (NfH), neurogranin (NGN) and YKL-40. CSF NfL levels, reflecting neurodegeneration, decreased slightly in the placebo and lowest-dose BIIB080, and slightly increased in the other BIIB080 treatment groups. All groups had slight increases in NfH. All BIIB080 treatment groups had decreases in YKL-40, a marker of

inflammation, while placebo group showed no change. NGN levels (reflecting synapses) were steady in the placebo and highest dose BIIB080 group, and decreased in the other BIIB080 groups.

In their presentation at ADPD 2023, the authors discussed their tau PET findings. They found that at the end of the MAD period of 25 weeks, there was a reduction in cerebral tau PET signal in patients who received BIIB080, while patients who received placebo had slight increases in tau PET signal. At the end of the LTE, wherein all patients received either 60 or 115 mg quarterly of BIIB080, they found decreases in tau PET signal in all brain regions assessed (Biogen Press Release).

A phase 2 trial with a primary endpoint of change in cognitive function is ongoing (NCT05399888).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Accumulation of tau- particularly hyperphosphorylated tau- is correlated with cognitive decline in AD and other tauopathies, and hyperphosphorylated tau is hypothesized to be one driver of neurodegeneration in AD and other tauopathies (DeVos et al., 2017, Mummery et al., 2023). Tau has therefore been a target of pharmacological strategies. Reduction of tau through use of tau heterozygotes or knockouts has been found to improve synaptic plasticity, cognitive impairment, synaptic loss, and premature mortality in a variety of AD models, including APP, hAPP, and APP/PS1 transgenic mice and direct injection of Aβ fibrils (Mummery et al., 2023, DeVos et al., 2013).

ASOs allow for reduction of tau rather than complete ablation. Use of MAPT ASOs in the PS19 mouse model of AD led to decreases in tau deposition and tau seeding capability, mitigated neuronal loss, and improved overall survival. Administration of the ASO could both prevent and also reverse tau pathology (DeVos et al., 2017). Suppression of tau expression through genetic and pharmacological approaches has also shown to reduce or reverse tau deposits and improve memory function in mouse models of AD (reviewed briefly by DeVos et al., 2017). Administration of BIIB080 was shown to reduce tau levels in nonhuman primates (Mignon et al., 2018).

In preclinical models, use of MAPT ASOs has also led to improvements in animal models of seizure and AD. Tau knockout models are less susceptible to chemically induced seizure activity and show reduced hyperexcitability and fewer spontaneous seizures when crossed with AD models. Knockdown of tau using ASOs in animal models reduced chemically-induced seizure frequency without affecting baseline motor or cognitive function (DeVos et al., 2013).

APOE4 interactions:

While the Phase 1b trial did include APOE4 carriers, no information has been shared as to any differential effects. Experimental studies indicate that APOE4 may exacerbate tau pathology (Koutsodendris et al., 2023), but the effects of reducing tau pathology in APOE4 carriers is unclear.

Aging and related health concerns: The physiological function of tau and effects of tau knockdown outside the central and peripheral nervous system are not well understood.

Types of evidence:

- None

Tau is predominantly expressed in neurons in the brain. Studies have found tau expression in the peripheral nervous system and in other tissues, but the role of tau in tissue other than the central nervous system is not understood. The effects of a MAPT ASO on function outside the brain is therefore not clear.

Safety: In the initial in-human study, BIIB080 appeared to be well-tolerated, with no drug-related serious events. Long-term effects of tau knockdown are not known.

Types of evidence:

- 1 randomized controlled trial
- 1 commentary
- 1 review
- 1 laboratory study

BIIB080 has been tested in one Phase 1b study involving 46 patients with mild AD, and is currently being tested in a Phase 2 study of 735 patients with MCI or mild AD (Mummery et al., 2023). In the Phase 1b study, all patients completed the multiple ascending dose portion. Three patients voluntarily withdrew from the study during the follow-up period; one from placebo group, one from the 60 mg BIIB080 group that received 4 total doses administered monthly, and one from the 115 mg BIIB080 group that received two doses quarterly.

In total, 75% of the participants in the placebo group reported an adverse event, and 94% of the participants treated with BIIB080 reported an adverse event. Most of the events were considered mild (88%), and the rest were considered moderate (12%). The percentage of adverse events though to be study drug-related was 44% in the BIIB080 treated groups and 0% in the placebo group. The incidence of mild adverse events was higher in the treated group than the placebo group; the incidence of moderate adverse events was similar between the two groups. There were two serious adverse events, both in the placebo group. There were no deaths, discontinuations, or dose-limiting adverse events.

The most common adverse event was post-lumbar puncture (LP) headache. Other reported adverse events were procedural pain, musculoskeletal pain, GI symptoms such as vomiting, nausea, and diarrhea, fatigue, runny nose, and dizziness. Many of these were more common in the treatment group,

though no event besides post-LP headache affected more than 20% of either group, many of them affecting less than 10% of participants. Two patients receiving BIIB080 experienced a mild confusional state and restlessness that had onsets within 48 hours post-dosing, and resolved within 4 days. These two patients had medical history of anxiety, and had been treated with psychotropic medication before the study began. There was one instance of moderate confusional state that the authors did not comment on in the publication.

In the exploratory CSF parameters, the authors found a slight decrease in CSF neurofilament light (NfL) levels in the placebo and 10 mg BIIB080 group, and a slight increase in CSF NfL in the other BIIB080 groups, though the increase was not dose dependent. While there were no differences between groups in the change of whole-brain volume over the course of the trial, the mean change from baseline in ventricular volume in all the BIIB080 treatment groups was greater than the mean change in the placebo group. The change was again not dose dependent. Ventricular enlargement was not seen on 'qualitative neuroradiological review of safety MRIs', and there were no clinical findings in the trial that are potentially associated with ventricular enlargement. While the interpretation of these findings is not straightforward, these are parameters that future studies should keep a close eye on (Mummery et al. 2023; Ljubenkov & Rabinovici, 2023).

It is worth noting that we do not understand the effects of loss of tau. While some studies have found little to no effects of tau knockout in animals, other studies have found deficits in tau knockout models including deficits in hippocampus long-term potentiation (LTP) and long-term depression and synaptic loss (Mummery et al., 2023; Sotiropoulos et al., 2017). Certain studies have also found that tau deletion in mice led to insulin resistance and metabolic changes (Marciniak et al., 2017). It is equally important to note though that these studies are in germline knockouts, meaning that at no point in their lifespan did they have tau present. ASO therapy reduces but does not eliminate tau, and it only removes tau after administration of the drug. And, the data from knockout animals is not consistent. These are potential unintended consequences to look for in ongoing and future trials.

Drug interactions:

Drug interactions of BIIB080 are not yet known.

Research underway:

NCT05399888 is a currently enrolling randomized, double-blinded, placebo-controlled Phase 2 trial investigating the safety, tolerability, and efficacy of BIIB080 in patients with MCI or mild dementia. The study plans to enroll 735 participants and will last for 72 weeks. Participants will be randomized to one of four groups: administration of placebo once every 12 weeks; administration of high dose BIIB080 once every 12 weeks; administration of low dose BIIB080 once every 24 weeks; or administration of high dose BIIB080 once every 24 weeks.

The primary outcome is dose-response change in cognition and function, as reflected by change in CDR-SB from baseline to week 76. The secondary outcomes include other measures of cognition and function, including the change from baseline to week 76 in: CDR-SB; ADCS-ADL-MCI; ADAS-Cog 13; MMSE; iADRS; and ADCOMS. Another secondary outcome is treatment-emergent adverse events and serious adverse events.

NCT04539041 is a randomized, double-blinded, placebo-controlled Phase I study of another intrathecally administered tau ASO, NIO752, in patients with a tauopathy called progressive supranuclear palsy (PSP). This study plans to enroll 66 patients for the 1-year study. All patients will receive 4 injections of the ASO or placebo control. The study group will test 3 doses of NIO752 as well as test different dosing frequencies; some patients will receive the 4 injections spaced out in a 3-month time period and then will be followed for 9 months, and others will receive their injections spaced out over 9 months and then be followed for 3 months. The primary outcomes are safety and change in severity score for the Columbia-Suicide Severity Rating Scale (C-SSRS). Secondary outcomes include pharmacokinetic measures of NIO752 in plasma and CSF.

Search terms:
Pubmed, Google: MAPT ASO, BIIB080, MAPTRX

- APOE4, dementia, AD

Websites visited for MAPT ASO, BIIB080:

- Clinicaltrials.gov
- Drugs.com
- PubChem
- Cafepharma

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